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APPLICATION NUMBER:

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NON-CLINICAL REVIEW(S)

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number: 210326
Supporting document/s: 1
Applicant's letter date: August 31, 2017
CDER stamp date: August 31, 2017
Product: Fulvestrant Injection 250 mg per 5 mL (50 mg/mL)
Indication: Advanced and metastatic breast cancer
Applicant: Fresenius Kabi, USA, LLC (FK USA)
Review Division: Division of Hematology Oncology Toxicology
(Division of Oncology Products 1)
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1 Executive Summary

1.1 Introduction

Faslodex (fulvestrant) Injection was approved in 2002 in the United States for the treatment of hormone receptor positive metastatic breast cancer in menopausal women with disease progression following antiestrogen therapy. Faslodex is supplied in sterile pre-filled syringes containing 50 mg/mL fulvestrant administered intramuscularly as two concurrent 5 mL injections on day 1, 15, 29 and once monthly thereafter. Currently, there are no approved therapeutic equivalents for Faslodex, and Faslodex is recognized as the reference listed drug (RLD).

Fresenius Kabi, USA, LLC (FK USA, the applicant) submitted on August 31, 2017 a new drug application (NDA) under the 505(b)(2) pathway to support marketing of Fulvestrant Injection for the following indications:

In a Monotherapy Modality:

- Hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, advanced breast cancer in postmenopausal women not previously treated with endocrine therapy, or
- HR-positive advanced breast cancer in postmenopausal women with disease progression following endocrine therapy.

In a Combination Therapy Modality:

- HR-positive, HER2-negative, advanced or metastatic breast cancer in combination with palbociclib or abemaciclib in women with disease progression after endocrine therapy.

Fulvestrant Injection has the same active ingredient (fulvestrant), strength, route, dosage, and dosing regimen as the RLD. Unlike the RLD, Fulvestrant Injection does not contain inactive ingredient benzyl benzoate but contains polysorbate 80, α -tocopherol, and a slightly higher content of castor oil.

1.2 Brief Discussion of Nonclinical Findings

In a non-GLP pharmacokinetic study in female rabbits, multiple fulvestrant formulations, including the formulation proposed for marketing (fulvestrant concentration of 50 mg/mL), were administered in female New Zealand White rabbits and showed similar bioavailability and exposure with relatively comparable injection site lesions. The study was previously reviewed under IND-122336.

In a GLP local tolerance toxicology study in female rabbits, a single intramuscular dose of FK Fulvestrant or Faslodex at 12.5 mg/kg was tolerated in female rabbits with no significant findings between the two fulvestrant formulations.

1.3 Recommendations

1.3.1 Approvability

Fulvestrant Injection is recommended for approval for the proposed indications from the pharmacology/toxicology perspective.

1.3.3 Labeling

None. The nonclinical sections of the proposed label have the same content as that of the RLD.

2 Drug Information

2.1 Drug

CAS Registry Number (Optional): 129453-61-8

Generic Name: Fulvestrant

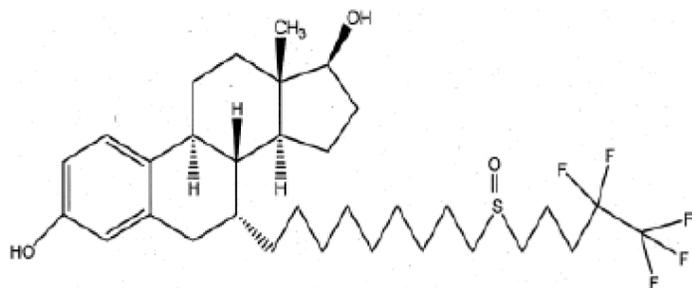
Code Name: None

Chemical Name: 7- α -[9-(4,4,5,5,5-pentafluoropentylsulfinyl)nonyl]estra-1,3,5-(10)triene-3,17- β -diol

Molecular Formula/Molecular Weight: C₃₂H₄₇O₃ F₅S / 606.77 g/mol

Structure or Biochemical Description

Figure 1 Chemical Structure of Fulvestrant



(Excerpted from the applicant's submission)

Pharmacologic Class: Estrogen receptor antagonist

2.2 Relevant INDs, NDAs, BLAs and DMFs

IND-122336 (Fulvestrant; the applicant): The applicant provided in the current NDA an authorization document (section 1.4.1) to allow the FDA to cross-reference IND-122336.

2.3 Drug Formulation

Table 1 Components and Composition of Fulvestrant Injection

Strength	250 mg/syringe			
Packaging Configuration	5 mL fill in a 5-mL glass syringe			
Syringe	5 mL, (b) (4) syringe barrel with luer tip, Type I Glass			
Stopper	(b) (4) plunger stopper			
Drug Product Name	Content (per mL)	Content (per syringe)	Function	Quality of ingredient
Fulvestrant	50 mg	250 mg	Therapeutic agent	N/A
Benzyl Alcohol	100 mg	500 mg	(b) (4)	NF
Alcohol (b) (4)	100 mg	500 mg		USP
Polysorbate 80	1.2 mg	6 mg	Solubilizing agent	NF
Alpha-Tocopherol	0.6 mg	3 mg	Stabilizing agent	NF
(b) (4)				
Castor Oil (Super Refined)	Q.S	Q.S	(b) (4)	NF
(b) (4)				

(Excerpted from the applicant's submission)

Table 2 Comparison of Drug Product Components of Faslodex (RLD) and Fresenius Kabi Fulvestrant Injection

Component	RLD, Faslodex® (mg per syringe)	Fresenius Kabi Fulvestrant Injection (mg per syringe)	Functionality
Fulvestrant	250	250	Therapeutic agent
Benzyl Alcohol	500	500	(b) (4)
Alcohol (b) (4)	500	-	
Alcohol (b) (4)	-	500	
Benzyl Benzoate	750	-	
Polysorbate 80	-	6	Solubilizing agent
Alpha-Tocopherol	-	3	Stabilizing agent
Castor Oil	Q.S.	-	(b) (4)
(b) (4) Castor Oil	-	Q.S.	(b) (4)

(Excerpted from the applicant's submission)

All excipients in FK Fulvestrant Injection are at or below the maximum potency in the FDA Inactive Ingredients Database (IID) for IM products, except for Castor oil ((b) (4) % w/v).

The castor oil content in the applicant’s formulation is at ((b) (4) % (w/v) which is above the FDA Inactive Ingredients Database (IID; 27.78%) level and the Faslodex level ((b) (4) %) but below the approved drug product ((b) (4) w/v). See table below.

The recommended doses and dosing frequencies for ((b) (4) include:

Judging from the results of the local tolerance study of FK Fulvestrant in female rabbits (see “General Toxicology” section below) and castor oil levels in FDA-approved products administered by the intramuscular route, this content of castor oil in FK Fulvestrant drug product is acceptable from the pharmacology/toxicology perspective.

Table 3 Comparison of Excipients between the Applicant’s Formulation with those in Faslodex (RLD) and Reference with FDA Inactive Ingredient Database (IID) Levels

Ingredient	Sponsor’s Formulation		Faslodex		IID Level
	(% w/v)	Single Dose (mg)	(%)	Single Dose (mg)	
((b) (4) alcohol	10	1000 ¹	10	1000 ¹	Intramuscular – 12%
Benzyl alcohol	10	1000 ¹	10	1000 ¹	Intramuscular – 10.962%
Benzyl benzoate	0	0	15	1500 ¹	NA
α-tocopherol	0.06	6	0	0	Intravenous – 0.064%
Polysorbate 80	0.12	12	0	0	Intramuscular – 12%
((b) (4) castor oil	QS	((b) (4)	QS	((b) (4)	Intramuscular ² – 27.78%

¹ Assumes a density of ((b) (4)

² Two FDA approved drug products for IM delivery contain higher concentrations of castor oil than the level approved in the IID, ((b) (4) % w/v and ((b) (4) % w/v. The castor oil in the Sponsor’s product ((b) (4) ((b) (4)

IID = FDA Inactive Ingredients Database; NA = not applicable; QS = quantum satis (the amount needed to complete the formulation)

(Excerpted from the applicant’s submission in IND-122336)

2.6 Proposed Clinical Population and Dosing Regimen

Clinical Population

In monotherapy modality:

- Hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced breast cancer in postmenopausal women not previously treated with endocrine therapy, or
- HR-positive advanced breast cancer in postmenopausal women with disease progression following endocrine therapy.

In Combination Therapy modality:

- HR-positive, HER2-negative advanced or metastatic breast cancer in combination with palbociclib or abemaciclib in women with disease progression after endocrine therapy.

Dosing Regimen

Fulvestrant Injection 500 mg is proposed to be administered intramuscularly (IM) into the buttock slowly as two 5 mL injections, one in each buttock, on Days 1, 15, 29 and once monthly thereafter.

A dose of 250 mg is proposed for patients with moderate hepatic impairment and administered IM into the buttock slowly as one 5 mL injection on Days 1, 15, 29 and once monthly thereafter.

2.7 Regulatory Background

None.

3 Studies Submitted

3.1 Studies Reviewed

Study Number	Title	Location
	Toxicology	
8309427* (Fulv-004-CNC)	Single-dose intramuscular injection toxicity study with FK fulvestrant in female rabbits	4.2.3.6 (mentioned only, without study report)

*This study was previously submitted under IND-122336 (SN-7) (section 4.2.2.2).

3.2 Studies Not Reviewed

None

3.3 Previous Reviews Referenced

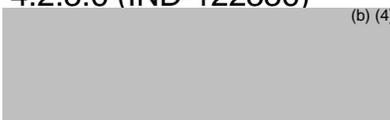
Study Number	Title	Location
	Pharmacokinetics	
1999-003*	Pharmacokinetic study of multiple fulvestrant formulations following intramuscular injection to female rabbits	4.2.3.6 (mentioned only, without study report)

*This study was previously submitted under IND-122336 SN-7 (Section 4.2.2.2), and was reviewed on December 29, 2014 by C.J. George Chang.

6 General Toxicology

6.1 Single-Dose Toxicity

Study title: Single-dose intramuscular injection toxicity study with FK fulvestrant in female rabbits

Study no.:	8309427 (Fulv-004-CNC)
Study report location:	4.2.3.6 (IND-122336)
Conducting laboratory and location:	 (b) (4)
Date of study initiation:	October 3, 2014
GLP compliance:	Yes
QA statement:	Provided
Drug, lot #, and % purity:	FK Fulvestrant; Lot #16HE0167; 100.7% purity Faslodex; Lot #KV802; purity not specified

Key Study Findings

A single intramuscular dose of FK Fulvestrant or Faslodex at 12.5 mg/kg was tolerated in female rabbits with no significant findings between the two fulvestrant formulations.

Methods:

Doses: FK Fulvestrant: 12.5 mg/kg fulvestrant
 Faslodex: 12.5 mg/kg fulvestrant
 Negative control (see below): 0 mg/kg
 Frequency of dosing: Once on Day 1
 Route of administration: Intramuscular (left hind limb, in 10-30 seconds)
 Dose volume: 0.25 mL/kg/dose
 Formulation/Vehicle: 0.9% Sodium Chloride for Injection, USP (sterile saline) for administration to the right hind limb
 Species/Strain: Hra:(NZW)SPF rabbits
 Number/Sex/Group: 6 Females/group
 Age: 17 weeks
 Weight: 2485 to 2668 g
 Satellite groups: None
 Unique study design: See table below
 Deviation from study protocol: None significant

Table 4 Study Design of Single-Dose Comparative Local Tolerance Study between Fulvestrant and Faslodex in Female Rabbits

Group ^a	No. of Females ^b	Dose Level (Right Side) (mg/kg)	Dose Concentration ^c (Right Side) (mg/mL)	Dose Level ^d (Left Side) (mg/kg)	Dose Concentration ^{d, e} (Left Side) (mg/mL)
1 (Control/FK Fulvestrant)	6	0	0	12.5	50
2 (Control/Faslodex®)	6	0	0	12.5	50

a Each animal served as its own control.

b Three animals/group were sacrificed on Day 2 of the dosing phase (approximately 24 hours postdose). The remaining animals were sacrificed following a 2 week observation period (Day 15).

c The control article (sterile saline) was injected to the right hind limb of each animal at a volume of 0.25 mL/kg/dose.

d Dose levels and concentrations refer to Fulvestrant active ingredient.

e FK Fulvestrant or Faslodex® formulation was injected to the left hind limb of each animal at a volume of 0.25 mL/kg/dose.

(Excerpted from the applicant's submission)

Observations and Results

Table 5 Measurements Made in the Local Tolerance Study in Female Rabbits

Measurements	Frequency
Mortalities and Moribundity, abnormalities, signs of pain or distress	Twice daily (am and pm)
Clinical Observation (Cageside)	Dosing Day: Approximately 1, 2, 4, and 24 hours postdose

Clinical observations (Detailed)	Predose: Once Dosing Day: Day 1: Prior to dosing Post-dosing Days: Day 2, 8, and 15
Body Weights	Predose: Three times Dosing Day (Day 1): Prior to dosing Post-dosing Days: Day 2, 8, and 15
Food Consumption (Qualitative)	Predose and Dosing Phase: Once daily
Dermal Irritation Scoring (Modified Draize technique): To score the two injection sites of each female rabbits for erythema, edema, atonia, desquamation, fissuring, and eschar)	Day 1: Prior to dosing and approximately 1, 2, 4, 24, 48, and 72 hours postdose Day 8 Day 15
Necropsy	Day 2: Three rabbits/group Day 15: All remaining survival rabbits
Macroscopic Examination: Injection sites and surrounding tissue	Day 2: Three rabbits/group Day 15: All remaining survival rabbits
Histopathology:	Injection sites and surrounding tissue

Mortality

No drug-related early mortalities occurred.

Clinical Signs and Feed Consumption

No drug-related clinical observations and effect on feed consumption were noted.

Table 6 Group Summary of Clinical Observations

Group Designation	Group 1	Group 2
Microscopic Findings	FK Fulvestrant	Faslodex
Dose (mg/kg, left hind limb)	12.5	12.5
n	6	6
Skin and pelage Scab, left hind foot		1

Body Weights

No significant drug-related differences in body weight or body weight changes were noted between the FK Fulvestrant and Faslodex groups.

Table 7 Group Mean Body Weights

Group Designation	Group 1	Group 2
Microscopic Findings	FK Fulvestrant	Faslodex
Dose (mg/kg, left hind limb)	12.5	12.5

Day 1 (n=6)	2560	2572
Day 2 (n=6)*	1↓	1↓
Day 8 (n=3)*	6↑	5↑
Day 15 (n=3)*	5↑	2↑

*Values expressed are percentage changes to Day 1 values.

Table 8 Group Mean Body Weight Changes

Group Designation	Group 1*	Group 2
Microscopic Findings	FK Fulvestrant	Faslodex
Dose (mg/kg, left hind limb)	12.5	12.5
Days 1-2 (n=6)	63↓	-21
Days 2-8 (n=3)	17↑	112
Days 8-15 (n=3)	54↓	-83
Days 1-15 (n=3)	22↑	59

*Body weight change values expressed are percentage changes from Faslodex group values (Group 2).

Gross Pathology

No drug-related gross pathology findings were noted.

A single pinpoint of red discoloration of the control-article injection site in one (1/6) FK Fulvestrant group, noted at the interim sacrifice. This finding was not drug-related.

Histopathology

Adequate Battery: Injection sites and surrounding tissue only

Peer Review: Performed

Histological Findings

Table 9 Drug-Related Microscopic Findings

Group Designation	Group 1	Group 2
Microscopic Findings	FK Fulvestrant	Faslodex
Dose (mg/kg, left hind limb)	12.5	12.5
Interim Sacrifice (n=3)		
Degeneration, muscle		
Minimal		3
Inflammation, granulocytic		
Minimal	1	
Slight		3
Moderate	1	
Terminal Sacrifice (n=3)		
Inflammation, mixed cell		
Minimal	1	2
Slight	1	

Dosing Solution Analysis

Not performed

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/s/

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